Amendments to the Drawings:

The attached sheet of drawings includes changes to Fig. 9. This sheet, which includes Fig. 9, replaces the original sheet. In Fig. 9, the recitation of "CD3" above the right panel has been corrected to "αCD3."

Attachment: Replacement Sheet (**Appendix A**)

REMARKS/ARGUMENTS

I. Interview Summary:

At the outset, Applicants thank Examiners Dave Nguyen and Maria Leavitt for the courtesy of a telephonic Examiner's Interview held January 13, 2006 with Applicants' representatives, Colleen Superko and Joseph J. Koipally.

Pursuant to 37 C.F.R. § 1.133(b), Applicants provide the following Interview Summary.

Prior to the interview, the Examiner had been forwarded a draft Response to the outstanding Office Action, which was substantially similar to the instant Amendment. At the telephonic interview, the draft Amendment was discussed.

The Examiners were informed that the claims printed in the patent that issued in the parent application (U.S. Patent No. 6,692,964) of the instant application were significantly different from the claims that were allowed by Examiner Nguyen. Applicants informed the Examiners that a Request for a Certificate of Correction had been filed to correct the claims of the issued patent.

In view of this discussion, the Examiners indicated that the independent claims of the instant application appeared allowable, and that they would review the claims in further detail and let Applicants know if there were any issues to be addressed.

Applicants thank Examiner Maria Leavitt for following up on January 19, 2006 after her review of the draft Response, and for her suggestions for minor amendments to some of the draft dependent claims. The Examiner's suggestions for claim amendments have been taken into account in the instant Response.

II. Applicants:

As a preliminary matter, Applicants note that the *Office Action Summary* incorrectly lists the Applicants of the instant application as Leeper *et al.* The correct Applicants for the instant application are **June *et al.*** Appropriate correction is respectfully requested.

III. Status of Claims:

Claims 22-53 are pending in the instant application.

Claims 22-53 are canceled herewith without prejudice or disclaimer of the subject matter contained therein.

Claims 54-100 have been newly added. The new claims are fully supported by the specification and the original claims. Specifically, support for the recitation "exogenous nucleic acid molecule" in claims 54 and 80 can be found at page 2, lines 1-3 and lines 10-12; page 5, lines 34-39; page 7, lines 9-10; page 8, lines 17-18; page 14, lines 20-21; and page 14, lines 26-27. Support for the recitation "compared with T cells not contacted with the stimulatory agent prior to introducing the exogenous nucleic acid molecule" in claims 54 and 80 can be found at page 7, lines 11-15, and in the working examples. Support for claim 55 can be found, for example, at page 10, lines 1-10. Support for claims 57-61 can be found at page 7, line 16 to page 8, line 36. Support for claims 62, 63, 73-76 and 91-93 can be found at page 9, lines 3-11 and in the working examples. Support for claims 97 and 98 can be found at page 11, lines 22-25 and page 14, lines 5-19. Support for claims 99 and 100 can be found at page 17, lines 9-11.

No new matter has been added by way of the instant amendments to the claims.

Upon entry of the instant amendment, claims 54-100 will be pending in this application.

IV. Drawings:

The Office Action objected to Fig. 9 for the label "CD3" instead of "αCD3" above the right panel (*see*, Office Action, page 2, second paragraph).

Fig. 9 has been amended to make the requested correction (*see*, **Appendix A**). Accordingly, the grounds for this objection have been overcome.

V. Claim Objections:

Claims 33-53 were objected to under 37 C.F.R. § 1.75(c) as being in improper form because a multiple dependent claim must be phrased in the alternative (*see*, Office Action, page 2, third paragraph).

Claims 33-53 have been canceled, and there are no multiple dependent claims among the newly added claims. Accordingly, the grounds for this objection have been overcome.

VI. Rejection Under 35 U.S.C. § 112, Second Paragraph:

Claim 22 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for recitation of the word "about" (*see*, Office Action, page 3, second paragraph).

Without acquiescing to this rejection, and solely to expedite prosecution, claim 22 has been canceled herewith. Therefore, Applicants address this rejection as it may apply to the pending claims.

Applicants note that newly added independent claims 54 and 80 do not recite the word "about." Instead, Applicants have used the phrase "less than" as suggested by the Examiner of the parent case, which issued as U.S. Patent No. 6,692,964.

Accordingly, Applicants aver that this rejection has been rendered moot.

VII. Rejections Under 35 U.S.C. § 112, First Paragraph:

(a) Claims 22-32 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement (*see*, Office Action, page 3, third paragraph). This rejection is specifically directed to the recitation of "stimulatory agents" in the claims.

As a preliminary matter, Applicants note that claims 22-32 are canceled herewith. Accordingly, Applicants address this rejection as it may relate to the newly added claims.

According to MPEP § 2163, to satisfy the written description requirement, an applicant's specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). The written description requirement prevents an applicant from claiming subject matter that was not described in the application as filed.

Applicants respectfully assert that the genus of "stimulatory agents" recited in the newly added independent claims 54 and 80 is in full compliance with the written description requirement.

In section 2 of the Detailed Description (*see*, pages 7-9), Applicants provide substantial written description support for a representative number of species that fall within the scope of the genus of "stimulatory agents." Specifically, the application describes the following stimulatory agents for use in the claimed invention:

(i) an agent which contacts the T cell receptor (*see*, page 7, line 22);

(ii) an agent which contacts the CD3 complex, *e.g.*, anti-CD3 antibodies (*see*, page 7, lines 22-25);

(iii) an agent that stimulates the CD2 complex, *e.g.*, anti-CD2 antibodies (*see*, page 7, lines 25-28);

(iv) an agent which provides a co-stimulatory signal in a T cell, *e.g.*, anti-CD28, a stimulatory ligand of CD28 such as B7-1 and B7-2 (*see*, page 7, line 35 to page 8, line 2);

(v) calcium ionophore, *e.g.*, A23187 (*see*, page 8, lines 8-10);

(vi) an agent which stimulates protein kinase C, *e.g.*, phorbol ester (*see*, page 8, lines 10-12);

(vii) a combination of calcium ionophore and phorbol ester (*see*, page 8, lines 12-14);

(viii) an agent that stimulates protein tyrosine kinases, *e.g.*, pervanadate (*see*, page 8, lines 14-16);

(ix) a polyclonal activator, *e.g.*, lectins such as PHA, ConA and PWM (*see,* page 8, lines 17-20);

(x) an antigen presented by an antigen presenting cell (*see,* page 8, lines 21-24);

(xi) a lymphokine, *e.g.*, IL-2 (*see,* page 8, lines 25-26);

(xii) a combination of an agent that provides a primary activation signal in T cells (*e.g.*, anti-CD3 antibody) and a lymphokine (*e.g.*, IL-2) (*see,* page 8, lines 26-31); and

(xiii) a superantigen, e.g., SEA, SEB, SEC, SED and SEE (*see,* page 8, lines 32-36).

In light of the above disclosure of a representative number of stimulatory agents, Applicants respectfully aver that one of ordinary skill in the art would readily recognize that Applicants were in possession of the genus of "stimulatory agents" at the time the instant application was filed. In fact, the Office Action acknowledges this fact, by stating, in relevant part: "[i]n the instant case, Applicant, provides ***a wide variety of agents*** that increase the expression of an exogenous nucleic acid molecule in T cells" (*see,* page 5, second paragraph, emphasis added). Furthermore, and importantly, the USPTO has previously concluded that the disclosure of the parent of this application sufficiently described the genus of "stimulatory agents" by issuing claims reciting this phrase (*see,* claims 1 and 16 of USPN 6,692,964).

The Examiner appears to be concerned that Applicants, have allegedly not determined the core structure of the stimulatory agents, and that some of the stimulatory agents used to increase expression of an exogenous nucleic acid molecule may not function as well as some of the other disclosed stimulatory agents.

Regarding the first concern, Applicants note that the Examiner-cited references WO94/29436 and Pullen clearly evidence that stimulatory agents of T cells were well known in the art at the time of the filing of the instant application. In this context, Applicants note that the Federal Circuit has stated that a patent specification need not teach, and preferably omits, what is well known in the art. *Hybritech Inc. v. Monoclonal*

Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). The instant application is not directed to the structure or sequence of stimulatory agents, but rather to methods of increasing the expression of an exogenous gene in a T cell. The structure and sequence of many of the species of the stimulatory agents provided in the instant application were known prior to Applicants' filing of the instant application. In any event, the structure and sequence of a stimulatory agent is not necessary so long as the agent can stimulate a T cell, which can easily be determined by well known T cell proliferation assays.

Regarding the second concern, Applicants note that the Examples clearly show that several agents described in the application as filed work perfectly well in the practice of the claimed invention (*see, e.g.*, Figs. 7, 8 and 16). Applicants note that even if some stimulatory agents were less effective than others, this would not be a basis for either a written description or enablement rejection. The Federal Circuit has held that a claim can encompass inoperative embodiments (*see, Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)). In the instant case, Figs. 8 and 16 clearly show that the combination of calcium ionophore and phorbol ester, the combination of anti-CD3 antibody and anti-CD28 antibody, and superantigens, can all stimulate proliferating T cells to increase expression of an exogenous nucleic acid molecule.

In summary, Applicants aver that they have provided adequate written description for the genus of stimulatory agents. In light of the foregoing remarks, Applicants respectfully request that this rejection under § 112, first paragraph, written description, be reconsidered and withdrawn.

(b) Claims 22-32 stand rejected under 35 U.S.C. § 112, first paragraph, as purportedly failing to comply with the enablement requirement (*see*, Office Action, page 7, first paragraph).

Applicants note that claims 22-32 are canceled herewith. Accordingly, Applicants address this rejection as it may relate to the newly added claims.

The Examiner stated that the specification is enabling for:

> A method for increasing the expression of an exogenous nucleic acid molecule comprising a gene in T cells, comprising:
>
> contacting the T cells *in vitro* with at least one stimulatory agent, wherein the T cells are proliferating prior to contact with the at least one stimulatory agent, forming stimulated proliferating T cells; and introducing the exogenous nucleic acid molecule into the T cells from step (a) *in vitro*, at most approximately 24 hours after contacting of said T cells, such that the expression of the exogenous nucleic acid molecule is increased in the T cells (*see*, Office Action, page 7, third paragraph).

Applicants note that the newly added claims are substantially similar to the claim recited above that the Office Action considers enabled.

Accordingly, Applicants respectfully request that this rejection under § 112, first paragraph, enablement, be reconsidered and withdrawn.

VIII. Rejections Under 35 U.S.C. § 102(e):

Claims 22-24, 26, 28, and 29 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Anderson *et al.* (U.S. Patent No. 5,399,346) (*see*, Office Action, page 10, first paragraph).

Claims 22-24, 26, 28, and 29 have been canceled herewith. Accordingly, Applicants address this rejection as it may relate to the newly added claims.

For a reference to anticipate a claimed invention in terms of 35 U.S.C. § 102, the prior art must teach ***each and every element*** of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

There are only two independent claims in the instant application: claims 54 and 80.

Independent claim 54 is directed to a method for increasing the expression of an exogenous nucleic acid molecule in T cells. The method comprises contacting the T cells

in vitro with at least one stimulatory agent, wherein the T cells are proliferating prior to contact with the at least one stimulatory agent, thereby forming stimulated proliferating T cells. The method further involves introducing the exogenous nucleic acid molecule into the stimulated proliferating T cells *in vitro*, less than 24 hours after contacting of said T cells, provided that the exogenous nucleic acid molecule is not introduced by particle bombardment, such that the expression of the exogenous nucleic acid molecule is increased in the T cells compared with T cells not contacted with the stimulatory agent prior to introducing the exogenous nucleic acid molecule.

Independent claim 80 is directed to a method for increasing the expression of an exogenous nucleic acid molecule in T cells, comprising contacting the T cells with at least one proliferative agent which stimulates proliferation of the T cells, forming proliferating T cells. The method further involves contacting the proliferating T cells *in vitro* with at least one stimulating agent, thereby forming stimulated proliferating T cells, wherein the at least one stimulatory agent is a combination of a first agent which provides a primary activation signal to the T cells and a second agent which provides a costimulatory signal to the T cells. The method further involves introducing the exogenous nucleic acid molecule into the stimulated proliferating T cells *in vitro*, less than 24 hours after contacting of said T cells, provided that the exogenous nucleic acid molecule is not introduced by particle bombardment, such that the expression of the gene is increased in the T cells compared with T cells not contacted with the stimulatory agent prior to introducing the exogenous nucleic acid molecule.

According to the Office Action, Anderson *et al.*

> ...culture primary T-cells in the presence of the antigen sperm whale myoglobin (SWM) and APC (col. 6, lines 46-50). When T-cells are cultured under these conditions, the antigen is presented to the T-cells in such a way that the T-cell receptor is stimulated and T-cell proliferate (col. 7, lines 12-15). Anderson further discloses how exogenous genes are introduced into murine derived T-cells ***after 3 days of antigen stimulation*** and proliferation of T-cells (col. 10, lines 1-7). (*see,* Office Action, page 10, last paragraph, emphasis added).

Anderson *et al.* do not anticipate Applicants' claimed invention because this reference does not teach each and every limitation of Applicants' claims. Specifically, Anderson *et al.* do not teach introducing an exogenous nucleic acid into stimulated proliferating T cells ***less than 24 hours*** after contacting of the T cells with at least one stimulatory agent. Instead, as the Office Action states (see, above), this reference teaches introducing "...exogenous genes into these 14.1 T cells, ***3 days*** after antigen stimulation..." (*see,* col. 10, lines 2-5 of Anderson *et al.*, emphasis added).

In addition, Anderson *et al.* do not teach, expressly or inherently, stimulating actively proliferating T cells prior to introducing an exogenous nucleic acid into the T cells. On the contrary, Anderson *et al.* teach that "[t]hese 14.1 T cells ***proliferate when challenged with SWM***" (*see,* col. 6, lines 46-47). Thus, the 14.1 T cells of Anderson *et al.* are ***not actively proliferating*** prior to contact with the at least one stimulatory agent, as required by Applicants' claims. Rather, these cells start to proliferate in response to the stimulatory agent.

Because Anderson *et al.* do not teach each and every limitation of Applicants' independent claims, Applicants respectfully submit that all of the present claims in the instant application are novel over Anderson *et al.* Therefore, Applicants request that this rejection be reconsidered and withdrawn.

IX. Rejections Under 35 U.S.C. § 103(a):

(a) Claims 22-25, 27, and 30-32 stand rejected under 35 U.S.C. § 103(a) as purportedly being unpatentable over Anderson *et al.* (U.S. Patent No. 5,399,346) in view of Nabel *et al.* (WO 94/29436) (*see,* Office Action, page 12, first full paragraph). As a preliminary matter, Applicants draw the Examiner's attention to the fact that WO 94/29436 is in the name of June *et al.*, ***and not Nabel et al.***

Applicants further note that claims 22-25, 27, and 30-32 are canceled herewith. Accordingly, Applicants address this rejection as it may relate to the newly added claims.

According to MPEP § 2143, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed above with respect to the § 102 rejection above, Anderson *et al.* do not teach or suggest all the limitations of Applicants' independent claims. The secondary reference, June *et al.*, which has been used by the Office Action for teaching other methods of T cell activation and stimulation, other than the use of antigen and APC taught by Anderson *et al.*, does not remedy the deficiencies of Anderson *et al.* outlined above.

Because the combination of Anderson *et al.* and June *et al.*, do not teach all the limitations of Applicants' claims, Applicants respectfully submit that this rejection under § 103 has been incorrectly applied. Accordingly, Applicants request that this rejection under § 103 be reconsidered and withdrawn.

(b) Claim 24 stands rejected under 35 U.S.C. § 103(a) as purportedly being unpatentable over Anderson *et al.* (U.S. Patent No. 5,399,346) in view of Pullen (Superantigens. In Encyclopedia of Immunology, I.M. Roitt and P.J. Delves, eds. Academic Press, New York, 1993, pages 1406-1408) (*see*, Office Action, page 14, first full paragraph).

Claim 24 has been canceled herewith. Accordingly, Applicants address this rejection as it may relate to the pending claims.

Again, as noted above, Anderson *et al.* do not teach or suggest all the limitations of Applicants' independent claims. The deficiencies of Anderson *et al.* are not remedied by the secondary reference, Pullen, which has been cited to show that superantigens are known to induce T-cell activation and proliferation.

Accordingly, Applicants respectfully submit that this rejection has been rendered moot. Thus, Applicants request that this rejection under § 103 be reconsidered and withdrawn.

X. Rejections Under the Doctrine of Obviousness-Type Double Patenting:

Claims 22-32 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-19 of U.S. Patent No, 6,692,964 (*see,* Office Action, page 15, second paragraph).

Applicants file herewith, as **Appendix B**, a Terminal Disclaimer under 37 C.F.R. § 1.321(c) over U.S. Patent No, 6,692,964.

In light of the above, Applicants respectfully request withdrawal of this rejection under the judicially created doctrine of obviousness-type double patenting.

XI. Information Disclosure Statement:

Applicants respectfully request that the Examiner consider and return an initialed copy of the PTO Form-1449 filed December 15, 2005.

CONCLUSION

Upon entry of the instant amendments to the claims, claims 54-100 will be pending in the instant application.

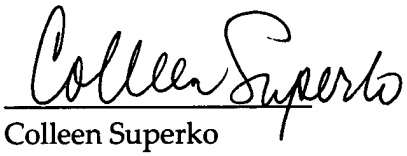
Applicants respectfully aver that these claims are in condition for allowance and respectfully request that a Notice of Allowance be issued.

Other than the excess claims fees, no additional fees are believed to be due in connection with this filing; however, if any fees are due, please charge our Deposit Account No. 08-0219.

If a telephonic interview would be helpful in expediting the prosecution of this application, the Examiner is invited to call the undersigned at the telephone number provided below.

Respectfully submitted,

Dated: January 19, 2006



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APPENDIX A

Attached is a Replacement Sheet for Figure 9 of the instant application.